REMARKS

The claims have been amended simply for clarification to note that the neoplastic disease is characterized both by growth at the primary tumor site and metastasis to secondary sites. Support for this language is found, for example, in column 7, lines 9, *et seq.*, and in the discussion throughout the specification. The amendment also includes clarification that mimicking the progression of neoplastic disease in humans includes mimicking its metastatic behavior. Support for this amendment is found not only in the specification as recited above, which recites exploring both primary and secondary tumor sites, but also by the Declaration of Robert M. Hoffman previously submitted and by the Second Declaration of Dr. Hoffman included with this response. The word "donor" has been deleted from the independent claims as lacking antecedent basis. No new matter has been added and entry of the amendment is respectfully requested. The proposed amendments are submitted in the context of a Request for Continued Examination under 37 C.F.R. § 1.114 and thus are timely submitted.

With respect to the amendment to state that mimicking the progression of neoplastic disease includes "the metastatic behavior of said neoplastic disease" in humans, respectfully, applicants believe this was already inherent in the claims. It has been made clear by the Federal Circuit in *In re Chu*, 36 USPQ2d 1089 (Fed. Cir. 1995) that the advantages of an invention need not appear even in the specification, much less in the claims. The claims in Chu were directed to an apparatus for controlling emissions of a fossil fuel fired boiler where the claim apparently differed from the prior art by requiring placement of the "SCR catalyst" inside the bag retainer of the filter bags. No advantage of doing so was recited in either the claims or the specification. In reversing the rejection of the claims as relying on a feature that was simply a matter of design choice, the Court rejected the Board's conclusion that arguments to the contrary were

unpersuasive because the "specification is virtually silent on the matter of any purported advantage to locating the catalyst within the bag retainer" and "does not state that the claimed location of the catalyst inside the bag retainer solves any particular problem or produces any unexpected result."

The Court stated that the "Board was required to consider the totality of the record and the Board was not free to disregard the evidence and arguments presented by Chu in response to the obviousness rejection" and in "apparently requiring Chu's evidence and arguments responsive to the obviousness rejection to be within his specification in order to be considered."

Thus, the Court has clearly held that there is no necessity explicitly to disclose, either in the specification or in the claims, the advantages that flow inherently from the invention practiced as claimed.

Nevertheless, since the amendment merely clarifies the inherent characteristic of the claimed methods, applicants are willing to call out the advantages of their model specifically.

As noted in the declarations of Dr. Robert Hoffman included in the present record, the claimed model does indeed mimic metastatic patterns found in humans.

The Tertiary Documents

There is really only one basis for rejection, although tertiary documents have been applied to claims 14, 16, 21 and 23 (Giovanella, *et al.*, disclosing models in rats) and claims 18 and 25 (Reddy, *et al.*, disclosing SCID mice). The teachings of these tertiary documents is acknowledged and it is believed that the patentability of the pending claims is not dependent on the use of rats in the model or SCID mice in the model; indeed, it is the purpose of the present reissue application to include these alternatives which were inadvertently not claimed in the issued patent.

Accordingly, this response will treat the rejection over the combination of Kyriazis, *et al.*, in combination with Otto, *et al.*, Wang, *et al.*, and McLemore, *et al.*, as applied to all claims.

The Invention Fills a Long Felt Need

The invention is directed to a model for neoplastic disease progression in humans which involves implanting intact tumor tissue orthotopically into an immunocompromised rodent. It is acknowledged that Kyriazis described an attempt to provide an accurate model of progression using implantation of intact tumor tissue subcutaneously, not orthotopically, in nude mice. McLemore provides what is intended as a model of disease progression where suspensions of cells are implanted orthotopically in the right lung. It appears that Otto is cited to show that the general technique described by Kyriazis for a number of human tumors is also applicable to renal tumors which are implanted as tumor pieces subcutaneously and Wang appears to be cited for the proposition that the technique of McLemore of orthotopic transplantation of cell suspensions of lung tumors is also applicable to colon tumors.

Thus, there is no question that, at the time of the original application on which the present application is based (1988), there were a number of studies attempting to establish models based on the approaches described in the cited documents. Kyriazis on page 3995, left-hand column, acknowledges studies employing transplanted human tumors as preserving the morphological, biological and biochemical characteristics of the tumor of origin at least one of which employed intact tumor pieces. McLemore on page 5137, right-hand column, acknowledges six papers which employ orthotopic models where cell suspensions were employed subcutaneously. However, prior to the invention, never the twain shall meet.

Applicants recognize that the model they are claiming in immunocompromised rodents is a combination of selected features of work describing implantation of intact tissue (but done

subcutaneously, Kyriazis and Otto) with orthotopic transplantation (but by injection of cells, McLemore and Wang). However, neither camp appears to have recognized the significance of that aspect of the contribution of the other which is employed in the present invention, or, as will be shown below in the case of Kyriazis, the feature of their own model that was employed in the invention. The Kyriazis paper was published in 1981, and the Wang paper was published in 1982. On this basis alone it is seen that after six years, the art had not seen a reason to combine the features of the invention to transplant intact tissues orthotopically, despite the availability of both techniques.

As noted in the review commissioned by the editors of "Cancer Drug Discovery and Development: Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials and Approval, 2nd Ed." Teiccher, B.A., and Andrews, P.A., eds., Humana Press, Inc., Totowa, NJ, supplied at the interview, and included herewith for the convenience of the Office as Exhibit 1, as early as the late 1960's, athymic mice had been employed to construct tumor models. In general, subcutaneous routes were employed, most of which utilized cell suspensions. Orthotopic models using cell suspensions were explored as early as 1982, *e.g.*, the Wang paper cited by the Office. As early as 1981, Kyriazis at least recognized the importance of the location of implantation (Kyriazis and Kyriazis, *Cancer Res.* (1980) 40:4509-4511), though within the context of subcutaneous implantation. Not until the present invention was made in 1988, however, was the combination of orthotopic implantation with implantation of intact metastasizing tumors thought of by anyone in the art. Although there was clearly a long-felt need for an accurate metastatic model, the construction of the accurate metastatic model of the present invention did not occur until the present inventors thought of it.

No Motivation to Combine

The Office objects to applicants' previous responses which are said to criticize the cited documents individually. Applicants point out these deficiencies in the cited documents not because applicants have misinterpreted the rejections as rejections for anticipation or because applicants fail to recognize that it is the combined teachings of the references that are important. These deficiencies are pointed out to show that the results obtained with the claimed models are unexpected and surprising in view of the notable lack of success of prior art models. This will further be addressed below; the argument begins with a lack of motivation to combine the documents cited.

It should first be noted, importantly, that the motivation required is that to actually make the combination. It is not quite accurate to state, as set forth on page 3 of the Office action, that "the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art." This statement of the law assumes that the combination will already have been made before the obviousness inquiry. This is not the case – one of ordinary skill in the art must be motivated to make this specific combination in the first place.

This is clearly set forth in the decision in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), cited previously in this record. The Court explicitly stated on page 1459 "the Board must explain the reasons one of ordinary skill in the art would have been motivated *to select the references* and to combine them to render the claimed invention obvious."

This distinction is critical. If one has already decided to combine the teachings of Kyriazis and McLemore, for example, one might find the model system of the invention at least obvious to try. But combining them, and then assessing the question of obviousness is not the law.

The Office accurately quotes Judge Baldwin's statement in *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). However, in that case, the applicant apparently argued that the primary reference simply did not suggest the particular arrangement of longitudinally offset doors in railway cars in combination with features disclosed in secondary references. That argument need not be made here; there is no argument made that Kyriazis does not alone suggest combination of an intact tissue implantation with orthotopic implantation; not even the Office takes the position that it does. The argument here is that there is no suggestion to select Kyriazis and McLemore from the multiplicity of models and combine the specified features of each.

The Office asserts that the motivation to combine Wang and McLemore with Kyriazis lies in the asserted disclosure by Wang and McLemore that orthotopic implantation is superior to other models. It may be true that the superiority of an orthotopic model was asserted; but the superiority of intact tumor vs. suspensions was not. After the fact, it may seem logical that intact tissue behaves more reliably than a cell suspension. But nothing has been shown in the art that leads to this conclusion. As explained by Dr. Hoffman at the interview, it was the more faithful behavior of tumors observed by the inventors themselves in 3-dimensional artificial matrices as compared to cultured tumor cells that led them to this conclusion. Kyriazis itself does not state, or even suggest, that intact tissue is a superior model. As explained at the interview, and verified by Dr. Hoffman's declaration, Kyriazis probably used intact tissue because it is more convenient than cell suspensions in a subcutaneous model.

McLemore postulates that the orthotopic model that was employed in the paper (cell suspensions) is superior to subcutaneous models. A fair reading of the paper, however, would lead one to conclude that in the view of McLemore, the model actually proposed is just fine. As stated by McLemore in the closing comments, "This intrapulmonary model has several advantages over other currently available models (no mention of subcutaneous) and should be of

particular value for future studies of lung cancer biology and treatment." Indeed, McLemore finds nothing wrong with the model proposed. Further, in comparing the results obtained orthotopically with a subcutaneous model, success of the orthotopic model was not evaluated with respect to faithfulness to disease progression patterns, but rather with respect to effectiveness in propagation of human lung tumor cells (page 5136-5137, bridging paragraph). In short, the reader of McLemore has no motivation to combine McLemore with anything else at all based on McLemore's touting of his own orthotopic model, not orthotopic models in general.

Perhaps the skilled reader of McLemore might be motivated to improve on McLemore's model by the fairly dismal results obtained in mimicking metastasis of human tumors when examined objectively. On page 5136, right-hand column, it is noted that 91% of the tumors in McLemore's model were localized to the right lung, whereas in only 1% of the cases did the tumors metastasize to the left lung and in only 6% of the cases did the tumors metastasize to the paratracheal area. These sites of metastasis are very common in human lung tumors; indeed, were this not the case, the death rate from lung cancer would be much lower since all that would need to be done is to remove the affected lung. The remaining lung would be sufficient to sustain at least some quality of life.

But even assuming that the skilled reader would note that the model proposed by McLemore is inadequate (it is pretty difficult to evaluate the model described by Wang as either good or bad), no reason is given as to why the reader would turn to Kyriazis to remedy this. And there is no reason. Like McLemore, Kyriazis is entirely content with the results obtained, indicating that Kyriazis is puzzled by reports by leading investigators on the absence of metastases (page 3995, left-hand column), though Kyriazis is unable to show typical patterns of metastasis as well.

The Office notes that Kyriazis' "primary interest is in lymph nodes and lungs" and that therefore, it is impossible to determine whether other tissues exhibited metastasis or not. However, this is not the case. At page 3995, right-hand column, it is noted that "tumors, regional and distant lymph nodes and representative sections *from various organs* were fixed in 10% buffered formalin solution. Removal and processing of lungs was done as described previously." Thus, it appears that lymph nodes and lungs were removed, but various organs, in addition were fixed in 10% formalin solution, and thus examined. Had metastases appears in these organs, they would have been reported. This too, is verified by the enclosed Hoffman declaration. Apparently some were found in the diaphragm as the Office notes, indicating that where metastases were seen, they were reported.

As noted in Dr. Hoffman declarations, the liver is (and was known in 1988) to be the primary site of metastases from colon. Apparently, none were found in the liver by Kyriazis when colon tumors are implanted. The metastatic patterns observed by Kyriazis were on their face deficient as admitted by Kyriazis himself "absence of metastases should be viewed within the context of the tumor host relationship and tumor biology rather than as evidence of benign tumor behavior." This is a cautionary statement to explain the obvious failure admitted by Kyriazis to observe metastases expected. Kyriazis viewed observation of metastases in lungs as:

> [A]n indication of the positive metastatic potential of the transplanted tumors regardless of the *absence of recognizable large tumor formations*. Failure to detect the latter may be related to various host factors, *e.g.*, mouse strain, health status of animals and site of transplantation, tumor size and growth rate and the biological characteristics of the original neoplastic growth from which the transplanted tumor originated. Furthermore, since metastases are not synchronous those taking place late in the life of the animal may not have the time required to reach the stage of detectability, being only microscopically seen as small aggregates or neoplastic cells within lymphatic channels and pulmonary vessels. (Emphasis added.)

In other words, Kyriazis recognizes that metastases that would have occurred in the human patients simply were not observed in the mouse. This is despite the fact that the tumors were allowed to grow to considerable size before the mice were sacrificed (see page 3995). (The calculated diameter of these tumors is on the order of 1.6 cm. using the formula provided.)

But Kyriazis does not present that as a drawback to the model presented. Kyriazis apparently is not suggesting any kind of metastatic models. So the reverse motivation (*i.e.*, Kyriazis sees the McLemore or Wang paper and would be motivated to modify the Kyriazis model) does not make sense. And the convenience of the intact tissue would go away because of the difficulty of the surgery required to do intact implantation orthotopically. Applicants are grateful that the Examiner, at the interview, recognized the delicacy of the techniques required in the invention method.

Thus, even if a reader of McLemore were persuaded by the inadequacies of the McLemore model (as evidenced by the unexpectedly low rate of metastasis) as a reason to improve the model, the skilled artisan would not be led to Kyriazis, whose results are even worse.

As noted as the interview, the use of intact tumor sections by Kyriazis is not considered by Kyriazis, at least in any manner discernable to the reader, to be advantageous over the use of cell suspensions. Instead, it is quite likely that the intact sections were used for convenience since it would not be necessary to alter the tumors to be transplanted to obtain cell suspensions. And while it is a straightforward matter to insert a sample of a tumor as an intact piece subcutaneously, it is not a trivial matter to insert such a sample orthotopically. All of the metastatic models based on orthotopic implantation until the present invention used the much more easily administered (in this context) cell suspensions.

Unexpected Results

This brings the discussion to the issue of unexpected results. As stated above, there is no motivation whatsoever to combine the teachings of Kyriazis with those of McLemore. Both orthotopic cell suspension models and subcutaneous intact tumor models had been in coexistence for at least six years prior to the date of the present invention, and only the applicants sought to combine these features, based on observations of *in vitro* tumor behavior in their laboratory. Their combination, as unsuggested as it was by the art, even if obvious to try, provided unexpectedly excellent results. These results have been set forth in the declaration of Dr. Robert Hoffman filed with the previous response indicating the great success of the claimed model. In view of the lack of success of both precursor models (only one element of each being used in the claimed model system), it could not have been predicted that the combination of orthotopic implantation with the use of intact tumor tissue would provide the successful results exhibiting faithful replication of the ability of tumors to metastasize in human patients as exhibited by the multiple publications from the laboratory employing this method, enclosed with the previous response. A more complete bibliography is enclosed herewith as Exhibit 2.

Commercial Success

As described in the enclosed Second Declaration of Dr. Robert M. Hoffman, the ability of the claimed model to mimic successfully the progress of tumors in humans has made it attractive commercially. The assignee of this technology, AntiCancer, Inc., has engaged in over 100 contracted studies as a service for large pharmaceutical companies and others seeking to evaluate candidate treatments and drugs in this model. The commercial success of this model is directly attributed to its unexpected and superior ability to mimic the behavior of human tumors.

Summary

Since it has been shown that the art does not suggest the invention, the invention fills a long-felt need, the invention provides unexpected results, and the invention has enjoyed considerable commercial success, it is believed that the rejection of the pending claims as obvious over the art is properly withdrawn.

CONCLUSION

The claims have been amended to clarify that metastasis is an integral part of the progression of neoplastic disease measured by the models of the claimed invention. Applicants acknowledge that the invention is a combination of a selected element from each of two commonly used models for neoplastic disease; for the reasons stated above, combination of these two features is not suggested by the art, but only by the invention itself and is thus not *prima facie* obvious. The Office has failed to show any motivation for combining these particular elements. Further, the results obtained with the claimed model are unexpectedly faithful to human metastatic patterns and have enjoyed considerable commercial success. Thus, it is believed that the rejection of the pending claims should be withdrawn and these claims be passed to issue forthwith.

In the event any matters can be clarified or otherwise resolved using a telephonic or other interview, a telephone call to the undersigned is respectfully requested. Applicants again express their appreciation for the thoughtfulness and care taken by the Examiner in providing a detailed Office action and in conducting the interview described above.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to

charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530.

Respectfully submitted,

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